Lung Cancer and Paraneoplastic Syndromes

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Disclosures

- None
Introduction

- Lung cancer is the most common cause of mortality WORLDWIDE
- 1.3 million deaths per year
- In U.S. 2012: 226,000 new cases

5 year Survival Rates

Cancer Survival Rates

The percentage of patients still alive five years after diagnosis, as seen below, has improved. But survival rates for lung cancer remain far lower for lung cancer patients than for patients with other cancers.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>1975-1977</th>
<th>2002-2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>68.3</td>
<td>99.2</td>
</tr>
<tr>
<td>Colorectal</td>
<td>50.1</td>
<td>64.3</td>
</tr>
<tr>
<td>Breast</td>
<td>75.1</td>
<td>89</td>
</tr>
<tr>
<td>Lung</td>
<td>12.3</td>
<td>15.9</td>
</tr>
</tbody>
</table>

Source: National Cancer Institute

Notes: 2002-2008 data reflect data from regions of U.S. with 28% of total population, while 1975-1977 data is drawn from regions with 9.5% of U.S. population. Survival rates include diagnoses at all stages.
Risk Factors

- **SMOKING**
- Environmental
  - Radon
  - Air pollution
  - Metals
- Asbestos
- Genetics
- HIV
- Pulmonary Fibrosis
- Radiation therapy

![Estimated Attributable Portion of Lung Cancer Cases by Cause](image-url)

Benign Lung Neoplasms

- **Epithelial Derived**
  - Papilloma (smoking, HPV)
    - Smoking, HPV
    - Squamous cell cancer
  - Micronodular Pneumocyte Hyperplasia
    - Tuberous sclerosis and/or LAM

- **Nonepithelial Derived**
  - Hamartoma
    - 50% of benign lung tumors
  - Solitary fibrous tumor
Malignant Lung Neoplasms

- **Non-small cell lung cancer (NSCLC)**-most common
  - Squamous cell
  - Adenocarcinoma-most common
    - “bronchoalveolar cell”
      - Atypical adenomatous hyperplasia, adenocarcinoma in-situ, minimally invasive adenocarcinoma
  - Large cell
  - Carcinoid

- **Small cell lung cancer (SCLC)**
  - Classic, large cell neuroendocrine, combined
  - Limited or Extensive

- **Primary pulmonary lymphoma**
  - Mucosa-associated lymphoid tissue type
  - Lymphomatoid granulomatosis
Figure 12-7. Incidence of types of lung cancer in smokers and nonsmokers.
Small Cell Lung Cancer

- Classic features:
  - Usually Central
    - 2/3 perihilar/hilar
    - 1/6 in main bronchus, 1/6 peripheral or apical
  - Most aggressive of all tumors with rapid doubling time
  - Early metastases (nearly 70% metastatic at presentation)
    - Liver 30-35%
    - Bone 40-50%
    - CNS 15%
  - Strongest association: Tobacco Use
  - Early response to therapy (chemo and radiation) but eventually becomes refractory
SCLC Staging

- **Limited Stage**
  - 30% of patients at presentation
  - Confined to one hemithorax
  - **Survival:**
    - Median survival is 15-20 months
    - 5 year ~ 10-15%

- **Extensive Stage**
  - 70% of patients at presentation
  - Extends beyond one hemithorax
  - **Survival:**
    - Median survival is 8-13 months
    - 5 year ~ 1-2%

Median survival without treatment is 2-4 months
Small Cell Lung Cancer

- Paraneoplastic syndromes
  - Ectopic ADH, ACTH
  - Eaton Lambert

- Treatment
  - Chemotherapy, XRT
  - Prophylactic cranial irradiation if attain complete response with initial treatment

- Survival not related to stage
Small Cell Pathology

• Small blue cells
• Scant cytoplasm
• Nuclear “molding”
• Extensive necrosis
• Cells contain neurosecretory granules
• Stains positive for CD56, synaptophysin, chromogranin, TTF-1
NSCLC: Squamous Cell

- Best prognosis of the major cell types
- Common Presentation:
  - Large central mass
  - Obstructive symptoms/signs,
  - May cavitate 10%
  - Locally invasive, but can metastasize widely
- Intermediate growth rate - late metastasis
- Associated with smoking
- Hypertrophic pulmonary osteoarthropathy (HPOA) is NOT most common with squamous anymore
- Hypercalcemia
- Pancoast syndrome
Squamous Cell Carcinoma

- Intercellular bridging
- Nesting formation
- Keratinization (well-differentiated type)
- “keratin pearls”
NSCLC: Adenocarcinoma

- Common Presentation
  - Peripheral in location
  - May metastasize widely before symptoms/signs develop
  - Not related to smoking
- Most common type of bronchogenic carcinoma in women NON-SMOKERS
- Slow growing but invades lymphatics and blood vessels
- May develop in or adjacent to fibrous lung “scar carcinoma”
- Many growth patterns exist: acinar, papillary, bronchioalveolar and solid w/ mucin formation, mixed subtype
NSCLC: Adenocarcinoma
Adenocarcinoma
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Immunoperoxidase staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Epithelial stains (e.g., CK 7, 20 variable), EMA (+), CLA, S-100, vimentin (-)</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>CK 7 (-); CK 20 (+)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>TTF-1 (+), Surf-A and Surf-B (+)</td>
</tr>
<tr>
<td>Other non-small-cell carcinoma</td>
<td>CK 7 (+), CK 20 (-), TTF-1 (-)</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>TTF-1 (+), chromogranin (+), NSE (+)</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>NSE, chromogranin, synaptophysin (+), epithelial stains (+)</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>HCG, AFP (+)</td>
</tr>
<tr>
<td></td>
<td>Oct4 transcription factor (+)</td>
</tr>
<tr>
<td></td>
<td>Placental alkaline phosphatase (+)</td>
</tr>
<tr>
<td></td>
<td>Epithelial stains (+)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>PSA (+), rare false (-) and (+)</td>
</tr>
<tr>
<td></td>
<td>Epithelial stains (+)</td>
</tr>
<tr>
<td></td>
<td>CK 7 (-), CK 20 (-)</td>
</tr>
<tr>
<td>Pancreas carcinoma</td>
<td>Ca^{19-9} (+), CK 7 (+)</td>
</tr>
<tr>
<td></td>
<td>Mesothelin (+), trifoil factor 1 (+)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>ER, PR (+)</td>
</tr>
<tr>
<td></td>
<td>Her-2-neu (+)</td>
</tr>
<tr>
<td></td>
<td>CK 7 (+), CK 20 (-)</td>
</tr>
<tr>
<td></td>
<td>Gross cystic fluid protein 15 (+)</td>
</tr>
</tbody>
</table>
NSCLC: Adenocarcinoma In-Situ

- **Presentation**
  - Usually peripheral
  - Ground glass or infiltrative appearance
  - Can be diffuse, unifocal, or multicentric
  - +/- bronchorrhea
  - Slow growing

- **Tumor may NOT invade stroma, pleura, or vasculature**

- **Lepidic growth**
  - Tumor cells line alveolar walls
Invasive Adenocarcinoma

- **Subtypes**
  - Nonmucinous (lepidic predominant-LPA)
  - Mucinous (invasive mucinous adenocarcinoma)
  - Mixed/Indeterminate (rare)

- **Increased risk with tobacco**
  - However – 30-40% are non-smokers
NCSLC: Large Cell

- 95% are undifferentiated
- Present as large masses (similar to squamous cell)
- Centrally located
- Fairly uncommon - 3% of all lung cancers
- Rapid Growth / Early metastasis
- Giant Cell variant - even more lethal with mean survival less than 6 months
Large Cell Carcinoma

- Large nuclei
- Moderate amt cytoplasm
Lung Cancer: Other types

- Undifferentiated carcinoma
- Bronchial gland tumors
  - Adenoid cystic
  - Mucoepidermoid
- Other rare tumors
  - Sarcomatoid carcinoma
  - Carcinoid
    - Typical
    - Atypical
Carcinoid (Bronchial Neuroendocrine Tumors)

- Neuroendocrine differentiation with relatively indolent clinical behavior
  - GI is most common site, lung is 2nd
- Carcinoid tumors represent 1-5% of all lung tumors
- Patients are usually younger than 40 years of age, nonsmoker
- Central airways
- Fewer than 2% associated with carcinoid syndrome
- Subclassifications include typical and atypical
  - Typical carcinoid: no p53 mutations or BCL2/BAX imbalance
    - Low grade, well-differentiated, slowly growing tumors
    - Rarely metastasize
    - Often cause endobronchial obstruction
  - Atypical: can see p53 mutations or BCL2/BAX imbalance
    - Intermediate-grade tumors with a higher mitotic rate and or necrosis
Carcinoid

- Carcinoids may arise centrally or peripherally
- Rarely exceed 3-4 cm
- Histologically: organoid, trabecular, palisading, ribbon or rosette-like arrangement
- On electron microscopy, the cells exhibit the dense core granules characteristic of other neuroendocrine tumors
Carcinoid

- Clinical manifestations come from intraluminal growth, capacity to metastasize and the ability of some to elaborate vasoactive amines
- **Most** bronchial carcinoids are non-secretory and do not metastasize
- **Some** are rarely functioning and capable of producing the “carcinoid syndrome” (diarrhea, flushing and cyanosis)
- Patients can develop persistent cough, hemoptysis, secondary infections, bronchiectasis and atelectasis, especially with bronchial obstruction
- Usually amenable to complete resection
Carcinoid tumors are often endobronchial

http://najms.net/v02i01p017f01h/
Pancoast Syndrome

- Superior sulcus tumor
- Horner’s syndrome
  - Ptosis
  - Miosis
  - Anhydrosis
- Brachial plexus
- Local erosion of vertebrae
Superior Vena Cava Syndrome

- Over 95% caused by malignancy
  - 5-10% lymphoma
- Histology: predominantly small cell or squamous
- May not be an “emergency” as previously thought
- Approach:
  - establish histologic diagnosis
  - institute therapy promptly (usually XRT)
  - steroids, diuretics, phlebotomy may help
Superior Vena Cava Syndrome
Metastasis

- Every organ system is susceptible to lung cancer metastasis
- Brain metastasis with deficits neurologically
- Bone metastasis with pain and fractures
- Spinal cord compression from bone or epidural metastasis
- Invasion of the marrow with cytopenias
- Liver metastasis causing biliary obstruction
- Lymph node metastasis in supraclavicular region
- Adrenal metastasis are common but rarely cause insufficiency
Clinical Evaluation

- Stage Patient: clinical stage and pathologic stage
- History and Physical
  - Cough, hemoptysis, exposures
  - Weight loss
- CT of chest and abdomen/pelvis with contrast,
- PET (sensitive for metastasis, recurrence)
- CT Brain/MRI Brain
- Bone Scan
- Review of any prior films very important
- Tissue diagnosis
  - Bronchoscopy (degree of obstruction/recurrence)
  - Mediastinoscopy
  - VATS/Thoracotomy
New Bronchoscopy Modalities

- **EBUS**
  - Endobronchial ultrasound will be able to get tissue samples from many more nodal stations without invasive surgical procedures

- **Navigational Bronchoscopy**
  - Via GPS mapping
PET Scans

- Whole Body Positron-emission Tomography
  - Nuclear medicine, functional imaging technique
  - 18F-fluorodeoxyglucose as a tracer (glucose analogue)
  - “Metabolic Imaging Technique”
    - Increased metabolism of glucose in all tumor cells
    - Carcinomas metabolize the tracer and “light-up” on the image
    - Concentrations of tracer imaged will indicate tissue metabolic activity by virtue of the regional glucose uptake
  - ~ 95% sensitivity for detecting primary bronchial tumors if lesion is greater than 1 cm!
Clinical Presentation

- 10% Asymptomatic at Time of Presentation!

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>45-74</td>
</tr>
<tr>
<td>Weight loss</td>
<td>46-68</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>37-58</td>
</tr>
<tr>
<td>Chest pain</td>
<td>27-49</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>27-29</td>
</tr>
<tr>
<td>Bone pain</td>
<td>20-21</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>8-18</td>
</tr>
</tbody>
</table>

Symptoms of lung cancer in over 3500 patients at presentation.

Associated Presentations

- Large Airway Obstruction
- Obstructive Pneumonitis
  - Obstructive pneumonia
- Atelectasis
  - Especially with endobronchial lesion
- Lymphangitic spread
- Pleural or Pericardial Effusion
- Hemopytsis
Lung Cancer Screening

Mayo Lung Project
• Randomized controlled trials have NOT demonstrated a reduction in mortality from screening with CXR or sputum cytology

Low Dose Spiral Chest CT Screening
• Radiation dose exposure is one third that of a standard CT scan
• NLST
  • Large randomized control trial of annual low-dose CT screening in patients with a 30+ pack year history of smoking (including those who quit in the last 15 years) demonstrated a decrease in lung cancer and all-cause mortality
  • *High rate of false + (non-cancer) findings causing additional testing and additional procedures
  • Yearly CXR has NOT been shown to be effective for lung cancer screening and should NOT be done (Grade 1A level of evidence)
NLST Criteria

- Age 55-74
- Current heavy (>30 pk-yr) or former smoker (quit within 15 yrs)
  - No CT within the last 18 months
  - Able to withstand lung cancer treatment
- Low dose helical CT scan
  - Single breath hold
  - 1.5 mSv (a standard CT is 8-12 mSv)
  - Read by thoracic radiologists
<table>
<thead>
<tr>
<th>Solid Nodules</th>
<th>&lt;6mm (&lt;100mm³)</th>
<th>6 to 8mm (100mm³-250mm³)</th>
<th>&gt;8mm (&gt;250mm³)</th>
<th>Comments Volumes are approximate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;6mm do not require routine follow-up, but certain high risk cases with suspicious morphology and/or upper lobe location may warrant 12 month follow up. (Recommendation 1A)</td>
</tr>
<tr>
<td>Low risk*</td>
<td>No routine follow-up</td>
<td>6 to 12 months CT, then consider 18-24 months CT</td>
<td>Consider 3 months CT, PET-CT, or tissue sampling</td>
<td></td>
</tr>
<tr>
<td>High risk*</td>
<td>Optional 12 months CT</td>
<td>6 to 12 months CT then 18-24 months CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiple</strong></td>
<td></td>
<td></td>
<td></td>
<td>Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (Recommendation 2A).</td>
</tr>
<tr>
<td>Low risk*</td>
<td>No routine follow-up</td>
<td>3 to 6 months CT, then consider 18 to 24 months CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk*</td>
<td>Optional 12 months CT</td>
<td>3 to 6 months CT, then 18 to 24 months CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsolid Nodules</td>
<td>&lt;6mm (&lt;100mm³)</td>
<td>≥6mm (&gt;100mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Single</strong></td>
<td>No routine follow-up</td>
<td>6 to 12 months CT to confirm persistence, then CT every 2 years until 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groundglass</td>
<td></td>
<td>In certain suspicious nodules &lt;6mm, consider follow-up in 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part-Solid</td>
<td>No routine follow-up</td>
<td>3-6 month CT to confirm persistence. If unchanged and solid component remains &lt;6mm: annual CT for at least 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiple</strong></td>
<td>3-6 months CT. If stable consider 2 and 4 year CT</td>
<td>3 to 6 months CT Subsequent management based on the most suspicious nodule(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple &lt;6mm pure groundglass nodules are usually benign, but consider follow-up in selected high-risk cases at 2 and 4 years (Recommendation 5A).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment of SCLC

- **LIMITED**
  - Radiation and Chemotherapy
  - PCI for complete responders
  - Occasionally surgery

- **EXTENSIVE**
  - Chemotherapy
  - PCI for complete responders
  - Radiation therapy for symptomatic metastasis (bone, epidural, brain)

Surgical treatment is rarely possible
NSCLC: Stage I and II Treatment

- Complete surgical resection
- Postoperative adjuvant chemotherapy for Stage II and possibly Stage Ib
- Patients who refuse chemotherapy or are not candidates may try radiation therapy
NSCLC: Stage III Treatment

- Locoregionally advanced disease due to primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0)

- Stage IIIA
  - Combined modality approach
    - Chemotherapy followed by surgery and postoperative chemo or radiation
    - 5yr Survival 10-30% with surgery alone
    - Multimodality treatments improve survival

- Stage IIIB
  - Surgery NOT an option
  - Combination chemo & XRT → 5yr survival 10%
NSCLC: Stage IV Treatment

- Chemotherapy or Palliative treatment only options
  - Palliative Therapy:
    - Brachytherapy
    - Laser Therapy
    - Airway stents and/or photodynamic therapy for airway obstruction
  - Radiotherapy → Palliative Treatment of bronchial obstruction, painful bone metastases, or CNS metastases
Treatment

The following are major contraindications to curative surgery or radiotherapy alone in patients with non-small cell lung cancer:

- Extrathoracic metastasis
- SVC, vocal cord/phrenic nerve paralysis
- Malignant pleural effusion
- Cardiac tamponade
- Tumor within 2cm of carina
- Contralateral lung metastasis
- Bilateral endobronchial tumor
- Metastasis to supraclavicular lymph nodes
- Contralateral mediastinal node metastasis
- Main pulmonary artery involvement
Treatment

- Chemotherapy: clearly effective for small cell, but relatively poor results for non-small cell carcinomas
- Laser Therapy: Nd-YAG laser for palliation of obstructing endobronchial lesions
Treatment: Tyrosine Kinase Inhibitors

Beyond histologic features, the status of molecular targets, such as the epidermal growth factor receptor (EGFR) gene, has been shown to correlate with response to treatment with EGFR tyrosine kinase inhibitors in patients with relapsed or refractory disease and in the first-line therapy setting.
Treatment: SPN

- Xray density that is surrounded by normal aerated lung, with circumscribed margins > 5cm
- 35% of such lesions are malignant (primary)
- “To resect or not to resect?” that is the question
- The following favors resection:
  - Young, large lesion, lack of calcification, chest symptoms, atelectasis, pneumonitis, adenopathy, growth revealed via x-rays
- Lack of growth over a > 2 year period and calcification would indicate a benign nature
- Dense central nidus, multiple punctate foci, “bull’s eye” (granuloma) and “popcorn ball” (hamartoma) calcifications suggest benign lesion
Mediastinal Mass

**Anterior mediastinum**
- Aneurysm
- Angiomatous tumor
- Goiter
- Lipoma
- Lymphoma
- Morgagni hernia
- Parathyroid tumor
- Pericardial cyst
- Teratoma
- Thymoma
- Thyroid tumor

**Posterior mediastinum**
- Aneurysm
- Bronchogenic tumor
- Enteric cyst
- Esophageal diverticula
- Esophageal tumor
- Neurogenic tumor

**Middle mediastinum**
- Bronchogenic cyst
- Bronchogenic tumor
- Lymph node hyperplasia
- Lymphoma
- Pleuropericardial cyst
- Vascular masses

Diagram showing the location of the mediastinum with labels for the trachea, esophagus, aorta, heart in pericardium, and diaphragm.
Benign Lung Neoplasms

- Represents < 5% of all primary tumors including:
  - Bronchial adenomas
  - Hamartomas (popcorn calcification)
  - Uncommon neoplasms
    - Chondromas, Fibromas, Lipomas, Hemangiomas, Leiomyomas, Teratomas, Pseudolymphomas
Bronchial Adenomas

- 80% are central
- Slow growing, endobronchial lesions
- Represent 50% of all benign pulmonary lesions
- 80-90% are carcinoids
- 10-15% are adenoid cystic tumors (cylindromas)
- 2-3% are mucoepidermoid tumors
Hamartomas

- Peak incidence age 60 with a preponderance in males
- Histologically they contain normal pulmonary tissue components in a disorganized fashion
- Peripheral, clinically silent and benign in behavior
- Radiological findings are “popcorn” calcification
- The lesions usually have to be resected if patient is a smoker – VATS can be used to minimize problems
Paraneoplastic Syndromes

- Clinical syndromes caused by underlying malignancy
- Mediated by humoral factors secreted by tumor cells or by responses to tumor antigen
- Associated with many types of lung cancer
- Can be the first manifestation of disease or disease recurrence
- 10% lung cancer patients present with a paraneoplastic syndrome
Paraneoplastic Syndromes

- **Adenocarcinoma**
  - Hypertrophic pulmonary osteoarthropathy

- **Small Cell Lung Cancer**
  - SIADH (Hyponatremia)
  - Cushing syndrome (ACTH producing)
  - Carcinoid syndrome
  - Neurogenic syndromes
    - Eaton-Lambert (proximal muscle)
    - Peripheral neuropathy

- **Squamous cell cancer**
  - Hypercalcemia (PTH related peptide)

- **Bronchial Carcinoid**
  - Cushing syndrome
Hypercalcemia

- Tumor secretion of PTH related peptide, increased active metabolite of vitamin D, and/or localized osteolytic hypercalcemia
- Occurs in 10-25% lung cancer patients
- Squamous Cell
- Median survival lung ca plus hypercalcemia: one month
- s/sx: polydipsia, GI sx-nausea, abd pain, mental status changes, dysrhythmia, hypotension, dehydration, renal dysfunction
SIADH

- Unregulated ADH production by tumor
- Leads to water retention by reabsorption in renal tubules
- Euvolemic hypo-osmolar hyponatremia
- s/sx: weakness, headache, nausea, altered mental status, coma, seizure
Cushing Syndrome

- Ectopic secretion of ACTH
- SCLC, bronchial carcinoid
- s/sx: weight gain, moon facies, acne, purple striae, proximal muscle weakness, peripheral edema, skin hyperpigmentation
Hypertrophic Pulmonary Osteoarthropathy

- Digital clubbing
- Painful symmetrical arthropathy (wrists, elbows, ankles, knees)
- Periosteal new bone formation (distal long bones)
- Adenocarcinoma
- Overexpression of vascular endothelial growth factor
Hypertrophic Pulmonary Osteoarthropathy
"Lose some weight, quit smoking, move around more, and eat the carrot."